Caffeine Enhancement of Saccharin but not Cyclamate Flavor Avoidance

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MASON, J. R. AND N. J. BEAN. *Caffeine enhancement of saccharin but not cyclamate flavor avoidance.* PHYSIOL BEHAV 39(6) 757–762, 1987.—The present experiments were designed to assess whether caffeine, a substance that potentiates human perception of some artificial sweeteners, might also enhance perception of such substances by rats. In Experiment 1, rats were given varied concentrations of saccharin, cyclamate, and caffeine in 2-choice tests. 'Indifference thresholds' for these substances were 3.9×10^{-4} M, 1×10^{-3} M, and 1.6×10^{-7} M, respectively. In Experiment 2, concentrations of saccharin and cyclamate just above and below indifference were used as stimuli in a flavor avoidance learning (FAL) paradigm. 'Suprathreshold' concentrations of saccharin and cyclamate produced reliable FAL while 'subthreshold' concentrations did not. In Experiment 3, rats were exposed to a low concentration of caffeine followed by presentations of subthreshold concentrations of saccharin or cyclamate as stimuli in a FAL paradigm. Saccharin FAL was observed but cyclamate FAL was not, suggesting that caffeine preexposure selectively potentiated detection of saccharin. In Experiment 4, animals were given saccharin or cyclamate with or without prior exposure to caffeine in a FAL paradigm. During subsequent tests, animals were presented with (a) saccharin or cyclamate following exposure to caffeine, (b) saccharin or cyclamate mixed with caffeine, (c) saccharin or cyclamate alone, (d) caffeine alone. Saccharin FAL was observed following caffeine preexposure, but mixing with caffeine had no effect. These findings of selective potentiation are consistent with previous studies of human sensitivity after caffeine preexposure. Moreover, the present results support the notion that inhibitory A1 adenosine receptors are involved in modulating the perceived intensity of some flavors.

Conditioned taste avoidance   Flavor profiling   Taste potentiation

METHYL XANTHINES, such as caffeine, theophylline and theobromine potentiate human sensitivity to acesulfam-K [12]. Caffeine also potentiates sensitivity to a variety of other artificial sweeteners, including neohesperidin, dihydrochalcone, D-tryptophan, thaumatin, stevioside, and sodium saccharin [11]. However, not all artificial sweetners are similarly affected, and tastants in this latter category include aspartame, and calcium cyclamate [11]. Because at least some bitter tastes (e.g., quinine hydrochloride, potassium chloride) are potentiated by methyl xanthines, Schiffman and her co-workers [11] have speculated that methyl xanthine potentiation of sensitivity to some artificial sweetners is related to their bitterness.

Two lines of evidence suggest that caffeine potentiation also may occur in the rat, a species for whom the perceptual characteristics of artificial sweeteners differ from those of humans. For example, low concentrations of saccharin are primarily 'sweet' ([7]; cf., [6]), and low concentrations of cyclamate, primarily 'bitter' [7]. One line of evidence is that caffeine enhances rat electrophysiological responsiveness to quinine hydrochloride [12]. The other is that chronic administration of theophylline to rats results in a reduction in pref-

erence thresholds for 0.25 M NaCl in water [4], and a reduction in rejection thresholds for 1.0% saccharin in food [5].

The present experiments were designed to assess whether brief (as opposed to chronic) exposures to caffeine might selectively enhance responsiveness to low concentrations of saccharin or cyclamate when these tastants served as conditional stimuli in a flavor avoidance learning (FAL) paradigm. The FAL methodology was used because of previous work demonstrating that rats given FAL are able to discriminate both the quality and quantity (i.e., intensity) of simple tastants, and tastants presented in 2-component [14] and complex [6,8] mixtures. In addition, FAL has been employed to describe the effects of thaumatin, a sweetness enhancer, on the perceived intensity of sucrose to rats [2].

EXPERIMENT 1

Experiment 1 was designed to assess the responsiveness of rats to concentrations of caffeine, gentain (a bitter flavoring), sodium saccharin and sodium cyclamate presented in 2-choice tests (flavor vs. distilled water). These data provided indifference thresholds (not to be confused with de-

TABLE 1
ANOVA RESULTS FOR EXPERIMENT 1

Na saccharin

Sessions (Concentrations): $F(8,32)=10.7$, $p<0.01$
2-Choice Tests: $F(1,4)=22.8$, $p<0.01$
Sessions × 2-Choice Tests: $F(8,32)=9.9$, $p<0.01$

Na cyclamate

Sessions (Concentrations): $F(10,40)=6.2$, $p<0.01$
2-Choice Tests: $F(1,4)=36.7$, $p<0.01$
Sessions × 2-Choice Tests: $F(10,40)=4.7$, $p<0.01$

Caffeine

Sessions (Concentrations): $F(13,52)=5.0$, $p<0.01$
2-Choice Tests: $F(1,4)=30.2$, $p<0.01$
Sessions × 2-Choice Tests: $F(13,52)=7.6$, $p<0.01$

Gentain

Sessions (Concentrations): $F(8,32)=1.7$, $p>0.25$
2-Choice Tests: $F(1,4)=2.3$, $p>0.25$
Sessions × 2-Choice Tests: $F(8,32)=1.9$, $p>0.25$

tection thresholds) that served as the empirical bases for Experiments 2–4.

METHOD

Subjects

Twenty adult male Charles River Sprague Dawley rats (260–285 g) were individually housed (cage dimensions: 17.7×24.2×17.7 cm) in a room with a 12/12 L/D cycle and an ambient temperature of 20±4°C. All animals were given free access to food (Wayne Lab Blox) and water for 2 weeks prior to the beginning of the experiment.

Procedure

During the third week, rats were given water daily for 15 min during the first hour of light, and for 30 min during the tenth hour of light. Water was presented in 30-ml graduated syringes fitted with metal sipper tubes [9]. The animals were ranked according to mean drinking (i.e., mean ml consumed) during the 15-min periods on days 5, 6, and 7, and assigned to 4 groups (n=5/group) that were matched with respect to water intake [6].

Concentration-response tests began the following day. Group 1 was presented with sodium saccharin concentrations; Group 2, sodium cyclamate concentrations; Group 3, caffeine concentrations; and Group 4, gentain concentrations. Flavors were presented in 2-choice tests (against distilled water), in descending and ascending series. For descending series, the starting concentrations of the flavors were:5×10^{-2} M sodium saccharin, 5×10^{-2} M sodium cyclamate, 2.5×10^{-2} M caffeine, and 0.02% gentain. Flavor concentrations were halved daily until animals failed to exhibit differential consumption. The concentration at which this event occurred was then presented a second time. If no differential consumption was again observed, an ascending series of flavor concentrations was presented. Conversely, if differential consumption was observed during the second test, a third test at the same concentration was given. De-
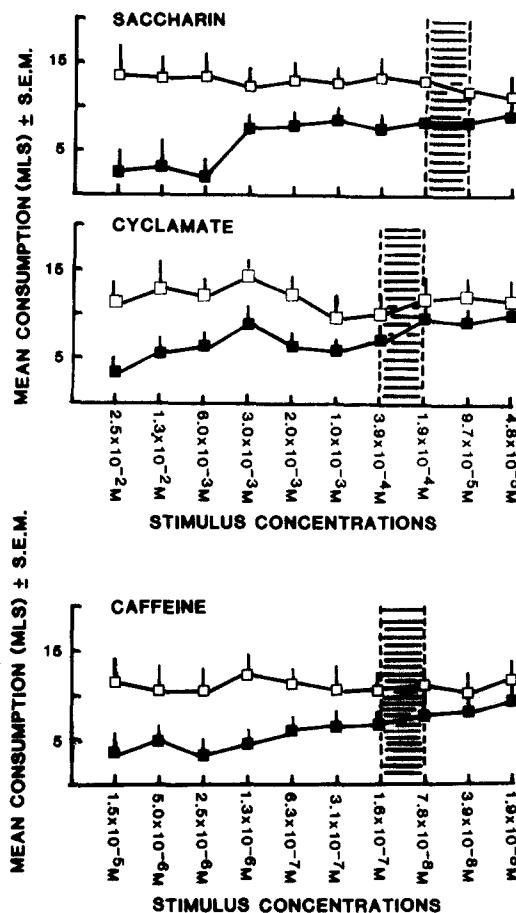

FIG. 1. Mean consumption of stimulus flavor concentrations (■) and distilled water (□) during 15 min 2-choice tests in Experiment 1. Shaded areas represent the concentration ranges in which no differential consumption was first observed. Vertical bars represent standard errors of the means.

pending upon the outcome of this test, descending trials continued, or an ascending series began. For ascending series, flavor concentrations were doubled on a daily basis until all concentrations given during the descending series had been presented. Descending and ascending series pairs were presented 4 times to each group of animals.

Analysis

Separate 2-way repeated measures analyses of variance (ANOVAs) were used to assess the results for each group. The factors in these analyses were (a) test sessions, and (b) consumption of stimulus versus consumption of distilled water. Tukey b-tests [17] were used to isolate significant differences among means.

RESULTS AND DISCUSSION

With the exception of gentain, there were significant differences among test sessions and within 2-choice tests for all flavors (Table 1). Also, in every case except gentain, the 2-way interaction between these terms was significant. Tukey tests revealed that rats drank less sodium saccharin than distilled water at concentrations equal to or greater than
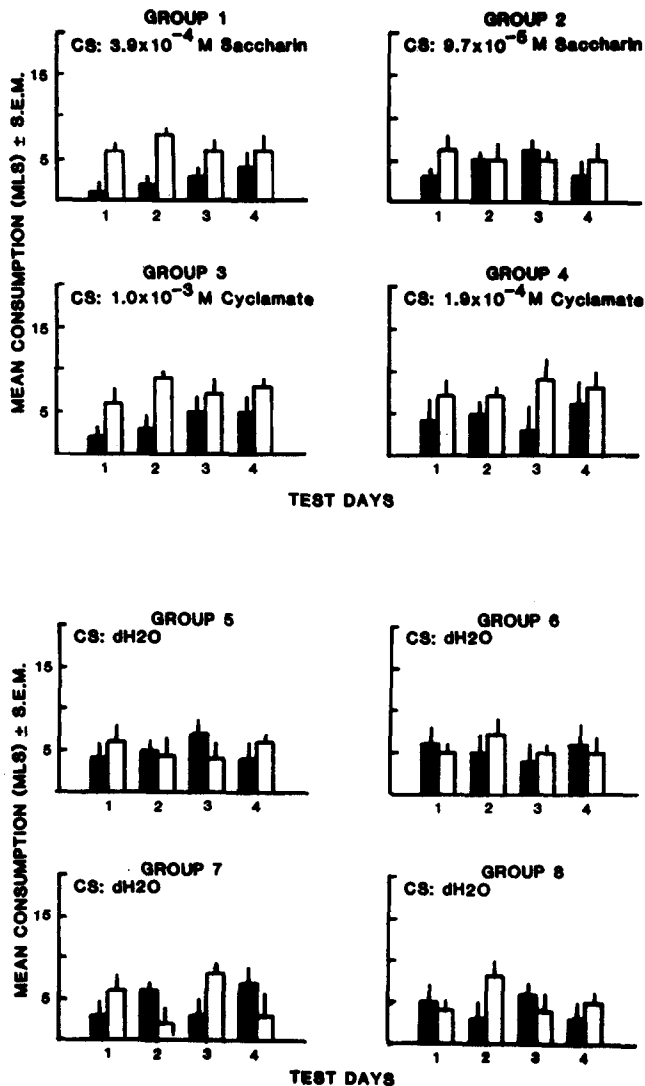
FIG. 2. Mean consumption of stimulus flavors (shaded bars) and distilled water (open bars) during 15 min 2-choice tests in Experiment 2. Vertical bars represent standard errors of the means.
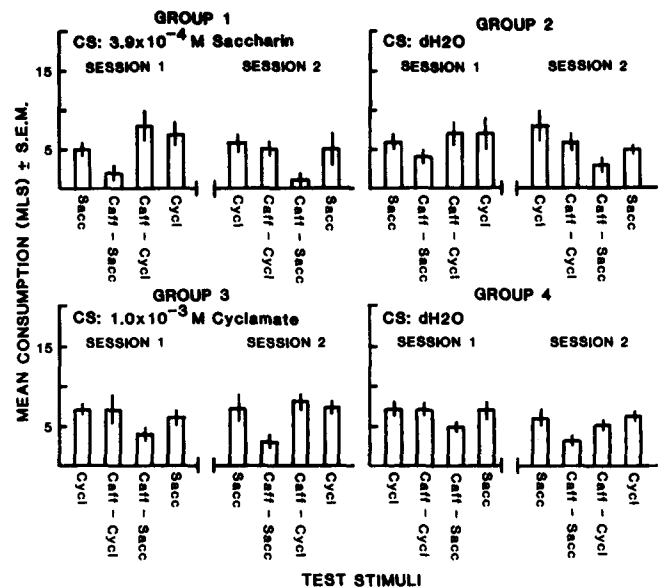

FIG. 3. Mean consumption of stimulus flavors during 15 min 1-choice tests in Experiment 3. Vertical bars represent standard errors of the means. Test stimulus abbreviations: Saccharin (Sacc); caffeine followed by saccharin (Caff-Sacc); cyclamate (Cycl); caffeine followed by cyclamate (Caff-Cycl).

1.9×10^{-4} M (Fig. 1). For sodium cyclamate, differential consumption was observed at concentrations greater than or equal to 3.9×10^{-4} M, while for caffeine, concentrations greater than or equal to 1.6×10^{-7} M produced differential responding. These values were operationally defined as 2-choice indifference thresholds for sodium saccharin, sodium cyclamate and caffeine. Threshold values were not interpreted as limits of detection. At least for saccharin, the lowest detectable concentration probably lies between 4×10^{-5} M and 1.2×10^{-4} M [15]. Instead, our goal was to provide an empirical basis for Experiments 2–4. If pre-exposure to caffeine in these later experiments resulted in differential responding to concentrations of a flavor below the indifference threshold, then that could be taken as evidence that caffeine had potentiated the perceived intensity of the flavor. Because no concentration of gentain produced reliable differential responding, this stimulus was eliminated from further consideration.

EXPERIMENT 2

Behavioral indifference in 2-choice tests is not necessarily synonymous either with flavor detection or recognition. The animals in Experiment 1 may have perceived both the quantity and quality of flavors presented at subthreshold concentrations. Experiment 2 was performed to assess whether sodium saccharin and sodium cyclamate, presented at concentrations just above and below the indifference thresholds, would serve as reliable conditional stimuli for CFA.

METHOD

Subjects

Forty-eight adult male Charles River Sprague Dawley rats (245–260 g) were housed and maintained as previously described.

Procedure

After 2 weeks, the animals were adapted to the water deprivation schedule, and assigned to 8 groups (n=6/group) on the basis of mean water consumption during the 15-min drinking period. On the day of conditioning, all groups were presented with stimulus (CS) fluids in 10-ml syringe-sipper tubes during the 15-min morning period. Groups 1 and 2 were given 3.9×10^{-4} M or 9.7×10^{-5} M sodium saccharin, respectively, while Groups 3 and 4 were given 1×10^{-3} M or 1.9×10^{-4} M sodium cyclamate. Groups 5–8 were given distilled water, as a control. After at least 5-ml of fluid was consumed, or after 1 hr had passed, each animal was given an intraperitoneal (IP) injection of 0.15 M lithium chloride (LiCl) at 100 mg/kg. On the day following conditioning, and during light on the next day, all animals were given free access to food and water to facilitate recovery from the conditioning trial. Water deprivation was begun again at dark onset of the second post-treatment day.

Over the next 4 days, all animals were presented with 4 2-choice tests between distilled water and their respective CS. Fluids were presented in 135-ml calibrated Richter tubes, the spouts of which were separated by about 10-cm when attached in pairs to the fronts of cages.

Analysis

A 3-way ANOVA with repeated measures on 2 factors was used to assess the results. The independent factor in this analysis was groups (8 levels), while the repeated factors were test sessions (4 levels) and CS consumption versus consumption of distilled water.

RESULTS AND DISCUSSION

The ANOVA revealed significant differences among groups, $F(7,40)=19.1$, $p<0.0001$, among test sessions, $F(3,120)=2.6$, $p<0.05$, and between CS consumption versus consumption of distilled water, $F(1,40)=15.0$, $p<0.001$. Also, there were significant 2-way interactions between groups and test sessions, $F(21,120)=5.4$, $p<0.01$, and test sessions and CS consumption versus consumption of distilled water, $F(3,120)=6.2$, $p<0.01$. Finally, the 3-way interaction among groups, test sessions and CS consumption versus consumption of distilled water was significant, $F(21,120)=3.7$, $p<0.01$. Post-hoc tests revealed that Groups 1 and 3 (those presented with the suprathreshold concentrations of saccharin and cyclamate) exhibited avoidance of their respective CS flavors during 3 and 2 test sessions (Fig. 2). Conversely, Group 2 (presented with the subthreshold concentraton of saccharin) exhibited CS avoidance only during the first test session ($p<0.05$). Group 4 (presented with the subthreshold concentration of cyclamate) and the control groups (Groups 5–8) failed to exhibit avoidance during any test session ($ps>0.25$). These results are consistent with the conclusion that Experiment 1 indifference thresholds for each of the 3 flavors approximated recognition thresholds.

EXPERIMENT 3

Experiment 3 was designed to assess whether preexposure to a low concentration of caffeine would enhance detection and subsequent avoidance of saccharin and caffeine when these flavors were presented at subthreshold concentrations.

METHOD

Subjects

Sixty adult male Charles River Sprague-Dawley rats (260–272 g) were housed and maintained as previously described.

Procedure

After 2 weeks, the animals were adapted to the water deprivation schedule and assigned to 4 groups (n=15/group) on the basis of mean water consumption during the 15-min drinking period. On the day of conditioning, Groups 1 and 3 were given 3.9×10^{-4} M sodium saccharin or 1×10^{-3} M sodium cyclamate, respectively, during the 15-min drinking period. These concentrations of each flavor exceeded the rejection thresholds established in Experiment 1, and elicited reliable conditioned avoidance in Experiment 2. Groups 2

and 4 were given distilled water as a control. After at least 5-ml of fluid was consumed, or after 1 hour had passed, each animal was given an IP injection of 0.15 M LiCl at 100 mg/kg. On the day following conditioning, and during light on the next day, all animals were given free access to food and water to facilitate recovery from the conditioning trial. Water deprivation was begun again at dark onset of the second post-treatment day.

Over the next 4 days, all animals were presented with 4 1-choice tests, in which subthreshold concentrations of sodium saccharin (9.7×10^{-5} M), sodium cyclamate (1.9×10^{-4} M), and caffeine (7.8×10^{-8} M) were used as stimuli. Although 2-bottle tests are more sensitive for detecting flavor avoidance [1], we used 1-bottle tests to encourage measurable consumption since the flavors used are relatively objectionable to rats. During the first test session, Groups 1 and 2 were presented with sodium saccharin, while Groups 3 and 4 were presented with sodium cyclamate. During the second test session, Groups 1 and 2 were presented first with caffeine and then sodium saccharin, while Groups 3 and 4 were presented first with caffeine and then sodium cyclamate. During the third test session, Groups 1 and 2 were given presentations of caffeine followed by sodium cyclamate, while Groups 3 and 4 were given caffeine followed by sodiûm saccharin. During the fourth test session, Groups 1 and 2 were presented with sodium cyclamate while Groups 3 and 4 were presented with sodium saccharin. The following day, Groups 1 and 2 were given an additional conditioning trial with 9.7×10^{-5} M sodium saccharin or 1.9×10^{-4} M cyclamate, respectively. Groups 2 and 4 were given an additional pairing of distilled water and LiCl. After 2 days free access to food and water, the deprivation schedule was reinstituted, and another 4 test sessions were given in an order opposite to that described above.

Analysis

The results of 1-choice tests were assessed in a 3-way ANOVA with repeated measures on 2 factors (weeks, stimuli). Subsequently, Tukey b-tests were used to isolate significant differences among means.

RESULTS AND DISCUSSION

There were significant differences among groups, $F(3,36)=12.6$, $p<0.0001$; Fig. 3, weeks, $F(2,72)=7.3$, $p<0.002$, and stimuli, $F(3,108)=80.7$, $p<0.0001$. Also, there was a significant 2-way interaction between weeks and stimuli, $F(6,216)=3.8$, $p<0.002$, and a significant 3-way interaction among groups, weeks and stimuli, $F(18,216)=3.5$, $p<0.0001$. Post-hoc tests revealed that all groups drank less saccharin after caffeine exposure ($ps<0.01$). This effect was strongest during the second week of testing ($ps<0.01$; Fig. 3). Among groups, Group 1 drank the least saccharin after caffeine exposure ($p<0.01$); other groups drank equivalent amounts. No similar effects of caffeine preexposure on cyclamate avoidance were observed for any group.

Caffeine preexposure enhanced sensitivity to low concentrations of saccharin. Sensitivity for cyclamate was not similarly affected. One interpretation of these results is that caffeine preexposure selectively potentiated the perceived intensity of the low concentration of saccharin to rats. An alternative explanation, however, is that caffeine remained in the mouths of the animals, and by combination with some aspect of saccharin taste, increased the overall perceptibility of test stimuli. Experiment 4 addressed this possibility.
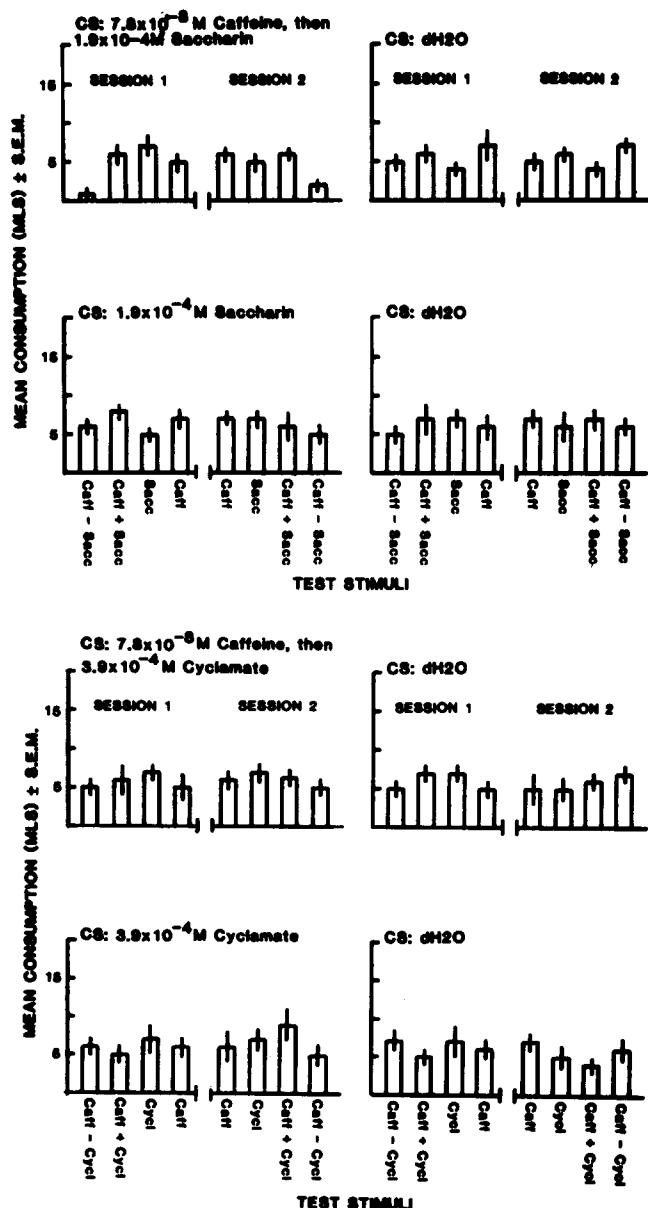
FIG. 4. Mean consumption of stimulus flavors during 15 min 1-choice tests in Experiment 4. Vertical bars represent standard errors of the means. Stimulus abbreviations: Saccharin (Sacc); cyclamate (Cycl); caffeine followed by saccharin (Caff-Sacc); caffeine mixed with saccharin (Caff+Sacc); caffeine followed by cyclamate (Caff-Cycl); caffeine mixed with cyclamate (Caff+Cycl); caffeine (Caff).

EXPERIMENT 4

One test between the alternatives presented above would be to condition animals by presenting saccharin following caffeine preexposure, and then to test animals with saccharin alone, caffeine alone, saccharin following preexposure to caffeine, and saccharin mixed with caffeine. If the animals were responding to the summated flavor of caffeine and saccharin, then preexposure to caffeine followed by saccharin and presentation of caffeine mixed with saccharin would produce similar results, or at least results different from pre-

sentation of the saccharin alone. In addition, presenting both caffeine and saccharin on the day of conditioning would permit assessment of whether animals perceive both the taste of the caffeine and the flavor. If animals perceive both, then they should exhibit generalization to both, since some evidence indicates that generalization of conditioned flavor avoidance is proportional to the degree to which components are perceived in a mixture [6,14].

METHOD

Subjects

Eighty adult male Charles River Sprague-Dawley rats (260–274 g) were housed and maintained as previously described.

Procedure

After 2 weeks, the animals were adapted to the water deprivation schedule, and assigned to 8 groups (n=10/group) on the basis of mean water consumption during the 15-min drinking period. On the day of conditioning, Groups 1 and 2 were pre-exposed to 7.8×10^{-8} M caffeine, and then given 1.9×10^{-4} M sodium saccharin or 3.9×10^{-4} M sodium cyclamate to drink. Groups 3 and 4 were given 1.9×10^{-4} M sodium saccharin or 3.9×10^{-4} M sodium cyclamate, respectively, without preexposure to caffeine. Groups 5–8 were given distilled water, as a control. All animals then were given an IP injection of 0.15 M LiCl at 100 mg/kg of body weight. After 2 days free access to food and water, the animals were given 4 days of 1-bottle tests. During these tests, animals were given (a) 1.9×10^{-4} M sodium saccharin or 3.9×10^{-4} sodium cyclamate following exposure to 7.8×10^{-8} M caffeine, (b) 1.9×10^{-4} M sodium saccharin or 3.9×10^{-4} M sodium cyclamte mixed with 7.8×10^{-8} M caffeine, (c) 1.9×10^{-4} M sodium saccharin or 3.9×10^{-4} M sodium cyclamate alone, and (d) 7.8×10^{-8} M caffeine alone.

On the seventh post-treatment day, all animals were given another conditioning session. This was followed by 2 days for recovery, and then another 4 days of 1-bottle tests, with test stimuli presented in the opposite order.

Analysis

The results of the 1-choice tests were assessed with a 3-way ANOVA with repeated measures on 2 factors (weeks, flavors). Subsequently, Tukey b-tests were used to isolate significant differences among means.

RESULTS AND DISCUSSION

While there were no differences among groups in overall consumption, $F(15,64)=0.9$, $p>0.25$; Fig. 4, there were significant differences between flavors, $F(3,45)=108.1$, $p<0.0001$. Also, there was a 2-way interaction between groups and flavors, $F(45,192)=14.7$, $p<0.0001$, and a 3-way interaction among groups, weeks, and flavors, $F(45,192)=1.9$, $p<0.002$. Post-hoc tests revealed that Group 1 animals drank less saccharin during testing when previously exposed to caffeine (ps<0.01). Group 2 animals (given cyclamate after caffeine on the day of conditioning) and Group 3 animals (given saccharin without caffeine preexposure on the day of conditioning) failed to exhibit this effect. No other statistical comparisons were significant.

The results of Experiment 4 are consistent with those of Experiment 3: caffeine preexposure selectively enhanced

sensitivity to sodium saccharin but not sodium cyclamate. In addition, the present findings demonstrate that caffeine preexposure effects are not the result of flavor summation: mixing caffeine with the saccharin had no enhancing effect. Finally, the results of the present experiment suggest that animals did not perceive the taste of caffeine during conditioning; no generalization was exhibited towards caffeine during subsequent test sessions. However, since exposure to sodium saccharin was interposed between caffeine preexposure and malaise, it is conceivable that the lack of caffeine generalization could reflect the temporal remoteness of caffeine to administration of the unconditioned stimulus.

An unexpected finding in Experiment 4 was that the consumption of the caffeine/saccharin mixture was not intermediate to consumption of saccharin following preexposure to caffeine and consumption of the saccharin alone. This result is inconsistent with observations by Tunaley *et al.* [16], who reported that the perceived odor intensity of ethyl butyrate and anisole were decreased when in solution with caffeine, and that this effect became more pronounced as the caffeine concentration increased. The concentrations of caffeine used to obtain these effects, however, ranged from 0.005 to 0.08 M, and thus were considerably higher than the concentrations used here.

GENERAL DISCUSSION

The present results demonstrate that the perceived intensity of saccharin to rats can be modified by caffeine preexposure. Experiments 1 and 2 established indifference thresholds for sodium saccharin, sodium cyclamate, and caffeine, and demonstrated that these thresholds approximated recognition thresholds. Experiments 3 and 4 showed that caffeine preexposure enhanced the perceived intensity of sodium saccharin but not of sodium cyclamate, suggesting that potentiation effects are selective. Additionally, the results indicated that enhancement of sodium saccharin was not a result of flavor summation between caffeine and saccharin. As such, the present results confirm and extend previous observations [11,12].

Schiffman and her co-workers [11] have speculated that methyl xanthine potentiation of artificial sweeteners is related to their bitterness. However, sodium saccharin may not be perceived by rats as bitter ([7]; cf., [6]), and the available evidence suggests that sodium cyclamate is perceived as bitter, and not sweet [7]. As such, one might have predicted an outcome of the present experiments opposite to that obtained (i.e., caffeine potentiation of cyclamate but not saccharin). Since only saccharin sensitivity was potentiated, we speculate that caffeine effects reflect peripheral (e.g., receptor) phenomena, while quality coding (i.e., 'bitterness,' 'sweetness') may reflect relatively more central events. Electrophysiological examination of neural responsiveness to the stimulus orders used in Experiments 3 and 4 might help to clarify this issue.

No obvious structural components clearly differentiate substances that are enhanced by caffeine from those that are not, but Schiffman, Diaz and Beeker [11] have reported that adenosine reverses potentiation effects. These investigators have hypothesized that reversal is caused by the activation of inhibitory A1 adenosine receptors. With regard to the present findings, it would be interesting to explore whether caffeine potentiation of perceived saccharin intensity by rats is similarly decreased by adenosine. It also might be interesting to assess whether caffeine might potentiate the intensity of tastants presented at low concentrations in flavor characterization experiments (e.g., [6]). Such potentiation effects could permit the flavor characterization of relatively insoluble materials, and/or toxic substances (e.g., rodenticides), that necessarily must be presented at low concentrations.

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